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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/449,077	11/24/1999	Dr. Thomas Hunig	12254/	5838

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EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	18

DATE MAILED: 08/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/449,077	Applicant(s) HUNIG, DR. THOMAS	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002 and 29 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *5-12,16-23 and 25-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,13-15 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 5/20/02 and 5/29/02 (Paper Nos. 17 and 15), are acknowledged.
Claims 1-4, 13-15 and 24 have been amended.
Claims 1-40 *are pending.*

Claims 5-12, 16-23 and 25-40 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-4, 13-15 and 24 *are under consideration in the instant application.*

2. This Office Action will be in response to applicant's arguments, filed 5/20/02 (Paper No. 17). The rejections of record can be found in the previous Office Action (Paper No. 13).

It is noted that New Grounds of Rejection are set forth herein.

3. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the form PTO-948 previously provided as part of Paper No. 13.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ***ABANDONMENT*** *of the application.*

4. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(d) Brief Summary of the Invention.
(e) Brief Description of the Several Views of the Drawing(s).
(f) Detailed Description of the Invention.
(g) Claim or Claims (commencing on a separate sheet).
(h) Abstract of the Disclosure (commencing on a separate sheet).
(i) Drawings.

Applicant is again requested to minimally provide the appropriate headers for the various sections found in the instant specification.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Applicant's amendments, filed 5/20/02 and 5/29/02, have obviated any rejections under 35 USC 112, second paragraph not reiterated below.

7. Claims 2-4, 13-15 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 2-4, 13-15 and 24 still recite the limitation "monoclonal antibodies" in the preamble. There is insufficient antecedent basis for this limitation in these claims. Independent claim 1, from which all other claims depend either directly or indirectly, recites a particular type of monoclonal antibody, a "human-compatible monoclonal antibodies". Thus the dependent claims do not further limit the independent claim, leading to confusion as to the metes and bounds of the dependent claims.

Applicant should amend the claims so that the preambles are consistent.

B) Claims 3-4, 13-15 and 24 are indefinite in the recitation of the phrase "in this way" because it is unclear what steps are encompassed by this phrase. Applicant should amend the claims to either recite steps, or if the intent is to refer to the preceding step, the phrase should be amended to indicate that step by reference to the letter (e.g., as in step "c" of the instant claims).

Applicant's argument, filed 5/20/02, that "in this way" is clear in context is acknowledged.

However, "in this way" can either refer to the preceding step, or can indicate that steps are missing, i.e., the details of the immunization step. Applicant is requested to either amend the claim, or to state clearly for the record that "in this way" refers to the preceding method step.

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-4, 13-15 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over June et al. (US Pat No. 5,858,358, of record) in view of Tacke et al. (Eur. J. Immunol. January 1997; 27:239-247, of record), and in further view of Applicant's acknowledgement on page 4 of the specification at lines 1-8 that production of hybridoma cells, humanization of antibodies, and production of monoclonal antibodies from humanized hybridoma cells was well known, as also evidenced by Bendig et al. (US Pat No. 5,558,864, of record).

The claims are drawn to human-compatible monoclonal antibodies to human CD28 which activate human T lymphocytes without occupancy of an antigen receptor (i.e., are "directly stimulating", and to hybridomas producing such antibodies.

Applicant's arguments, filed 5/20/02, have been fully considered but have not been found convincing, essentially for the reasons of record in Paper No. 13.

Applicant asserts that the Examiner admits that the anti-human CD28 antibodies of June et al. do not directly activate human T cells. However, the Examiner's comments of record were the following:

> June et al. teach antibodies to human CD28, and the production of hybridomas producing anti-human CD28 antibodies (see entire document, especially columns 5-6 and 12-17). June et al. teach that cells transfected with human CD28 can be used to immunize mice and the hybridomas producing anti-human CD28 antibodies isolated (e.g., columns 12-17). June et al. also teach that antibodies which stimulate T cell proliferation are highly desirable because they can be used to expand T cells for treatment of individuals with low numbers of T cells, as occurs in HIV infection, as well as to expand T cells for therapies requiring stimulation of an immune response (see especially columns 18-20).

> June et al. do not teach humanized antibodies or test whether any of the antibodies to human CD28 are able to directly stimulate T cells.

The Examiner did not admit that the antibodies of June et al. are not "directly stimulating", but rather observed that June et al. did not test for this activity.

With respect to the teachings of Tacke et al., the Examiner has previously observed that

> Tacke et al. teach the production of hybridomas secreting a rat antibody to human CD28 and the characterization of the rat antibody JJ316 (see entire reference, e.g., Abstract). Tacke et al. teach that the rat antibody JJ316 is specific for rat CD28 and can activate proliferation of all T cell subsets without T cell receptor occupancy (see entire document, especially Figure 2 and section 3.4). Tacke et al. also teach that the ability of the JJ316 antibody to "directly" stimulate is due to a difference in fine specificity versus other anti-CD28 antibodies that do not directly stimulate; and that antibodies with this fine specificity can be generated by immunizing with CD28 transfected cell lines more readily than by immunizing with T cells which naturally express CD28 (see especially page 245, 2nd column).
>
> Tacke et al. do not teach hybridomas producing antibodies to human CD28 or humanization of anti-CD28 antibodies.

Applicant is correct in pointing out that the reference to an antibody to human CD28 in the first line is clearly an inadvertent misstatement in view of the correct references elsewhere in the rejection to the antibodies of Tacke et al. being specific for rat CD28.

The Examiner has further argued that

> [] given the teachings of Tacke et al. that directly stimulating antibodies can be produced by immunizing with a cell line transfected with human CD28, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen the antibodies taught by June et al. (or to produce additional antibodies) for those monoclonal antibodies and the hybridomas producing them which are specific for human CD28 and which directly activate human T cells without occupancy of the T cell antigen receptor. One would have been motivated to screen for such antibodies and hybridomas producing them in order to derive antibodies that could be used without anti-CD3 antibodies in the methods of June et al. to expand T cells for human therapy. Given the teachings of Tacke et al. that anti-CD28 antibodies which directly stimulate T cells without occupancy of the T cell receptor are produced using immunization strategies based upon transfected cell lines rather than T cells, and the teachings of June et al. that transfected cell lines could be and were used; one of ordinary skill in the art would have had a reasonable expectation that directly stimulating antibodies specific for human CD28 were produced or could be produces using the method of June et al. and could be identified as taught by Tacke et al.

Applicant has argued that the rejection of record constitutes an "obvious to try" rejection. However, the ultimate conclusion of law that claimed subject matter as a whole would have been obvious under 35 USC 103 may at times properly be drawn from an inference of fact arising from prior art teachings which could be considered an inference that it would be "obvious to try" that which is claimed. In re O'Farrell, 853 F.2d 894, 7 USPQ 2d 1973 (Fed. Cir. 1988); Contour Saws Inc. v. Starrett Co., 444 F. 2d 433, 170 USPQ 433 (Ct.App. 1977); In re Marzocchi, 439 F. 2d 220, 169 USPQ 367 (CCPA 1977); In re Lindell, 385 F. 2d 435, 155 USPQ 521 (CCPA 1967).

The Examiner acknowledges that the instant rejection is not a rejection of anticipation because June et al. clearly do not teach humanization (i.e., creating a "human-compatible) of their anti-human CD28 antibodies. However, that the antibodies produced by June et al. would have the instantly recited property of specificity for human CD28 and the ability to activate human T lymphocytes of several to all subgroups without occupancy of an antigen receptor of the human T lymphocytes and thus antigen-non-specifically is germane to the instant rejection under 35 USC 103(a) because these are expected properties of the antibodies produced by June et al. given the method steps used.

The Examiner has previously provided a proper motivation for screening the antibodies of June et al. to identify these expected properties in order to identify antibodies that could be used without anti-CD3 to expand T cells for human therapy, as taught by June et al. The Examiner has also provided a reasonable expectation of successful isolating antibodies having the instantly recited properties because Tacke et al. teach that the instantly recited properties are expected properties of antibodies produced using transfected cells.

With respect to the newly added limitation that the human-compatible antibodies specific for human CD28 also be effective for treating a disease with pathologically reduced numbers of CD4 T cells or an autoimmune disease, June et al. also teach that the T cells expanded for human therapy, noted supra, are used to treat the reduced T cell numbers that result from HIV infection (see especially columns 18-20).

Thus contrary to Applicant's assertions, there is no need to modify the teachings of June et al. June et al. teach antibodies which, based upon the teachings of Tacke et al., are expected to have all the instantly recited properties except the limitation that the antibody be "human compatible", as recited in claim 1.

As previously acknowledged,

> neither Tacke et al. nor June et al. teach humanization of the antibodies to human CD28.

However, the Examiner has previously noted and Applicant does not argue the point that

> as acknowledged by Applicant on page 4 at lines 1-8, methods of humanizing antibodies were well known in the art at the time the invention was made, as evidenced by Bendig et al. Bendig et al. also teach that human-compatible antibodies are desirable in order to reduce immunogenicity and improve antibody half-life and efficacy when administered to a human (see entire document, especially columns 21-22).
>
> It would have been obvious to the ordinary artisan at the time the invention was made to humanize the monoclonal antibodies specific for human CD28 taught by June et al., including those antibodies which directly activate T cells without occupancy of the T cell antigen receptor. Given the art-recognized methods of humanizing antibodies, as acknowledged by Applicant and as evidenced by Bendig et al., the ordinary artisan would have had a reasonable expectation of success. In addition, Bendig et al. teach that the ordinary artisan at the time the invention was made was motivated to humanize antibodies in order to produce improved therapeutics.

Further, the Examiner has previously noted and Applicant does not argue the point that

> [w]ith regards to the various method steps recited in the production of the monoclonal antibodies and hybridomas, it is noted that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection of record is maintained as it applies to the instantly amended claims.

10. Claims 1-4, 13-15 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siefken et al. (Cell. Immunol. February 1997; 176:59-65, of record), in view of Applicant's acknowledgement on page 4 of the specification at lines 1-8 that production of hybridoma cells, humanization of antibodies, and production of monoclonal antibodies from humanized hybridoma cells was well known, as also evidenced by Bendig et al. (US Pat No. 5,558,864).

The claims are drawn to human-compatible monoclonal antibodies to human CD28 which activate human T lymphocytes without occupancy of an antigen receptor, and to hybridomas producing such antibodies.

Applicant's arguments, filed 5/20/02, have been fully considered but have not been found convincing, essentially for the reasons of record in Paper No. 13.

Siefken et al. teach the production of hybridoma-produced antibodies to human CD28 and that the BW 828 antibody could activate human T cells without co-engagement of the T cell antigen receptor/CD3 complex (see entire document, especially "Materials and Methods" and "Discussion").

Applicant argues that the specification distinguishes the instantly recited antibodies from those of Siefken et al. in Example 3 of the specification, which notes that unlike the antibodies of Siefken et al., the antibodies of the instant invention do not require crosslinking by means of a second antibody.

However, the limitation of not requiring crosslinking argued by Applicant is not recited in the instant claims, which instead only require that activation occur without occupancy of the antigen receptor.

Applicant further argues that the antibodies of Siefken et al. do not stimulate "several to all subgroups" of T cells because Siefken et al. show that primarily T cells having a memory phenotype were stimulated.

However, Figure 4 shows that while memory (CD45RO+) cells certainly proliferated more readily, CD45RA+ cells also show some increase in proliferation (compare white boxes of Figure 4). Further, depending upon which "sub-group" one is considering, there are other T lymphocyte subsets encompassed within those cells that are CD45RO+. For example, one may subset CD45RO+ cells based upon their T cell receptor gene usage, chemokine receptor expression, expression of CD25, etc. The instant claims do not require any particular "sub-group" and therefore are not at present distinguished from the teachings of Siefken et al.

Siefken et al. do not teach humanization of anti-CD28 antibodies.

However, as acknowledged by Applicant on page 4 at lines 1-8, methods of humanizing antibodies were well known in the art at the time the invention was made, as evidenced by Bendig et al. Bendig et al. also teach that human-compatible antibodies are desirable in order to reduce immunogenicity and improve antibody half-life and efficacy when administered to a human (see entire document, especially columns 21-22).

It would therefore have been obvious to the ordinary artisan at the time the invention was made to humanize the monoclonal antibodies specific for human CD28 taught by Siefken et al. Given the art-recognized methods of humanizing antibodies, as acknowledged by Applicant and as evidenced by Bendig et al., the ordinary artisan would have had a reasonable expectation of success. In addition, Bendig et al. teach that the ordinary artisan at the time the invention was made was motivated to humanize antibodies in order to produce improved therapeutics.

With regards to the various method steps recited in the production of the monoclonal antibodies and hybridomas, it is noted that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection of record is maintained as it applies to the instantly amended claims.

11. No claim is allowed.

12. This application contains claims5-12, 16-23 and 25-40 drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

13. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
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August 26, 2002

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